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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR# 0052429

DATE: January 26, 05

MEMORANDUM:

SUBJECT: **INDOXACARB** - Review of Studies (MRIDs 45911401, 45911402, 45911403)

PC Nos.: 067710
DP Barcode Nos: 300062
Submission Nos:
Tox. Chem. No.:

From: Pramod S. Terse,DVM,PhD,DABT
Registration Action Branch I
Health Effects Division (7509C)

To: Daniel Kenny, Risk Manager
Registration Division (7505C)

Thru: P. V. Shah, Branch Senior Scientist
Registration Action Branch I
Health Effects Division (7509C)

The Registration Action Branch I (RAB 1) has reviewed Dermal Penetration Study in Rat (MRID 45911401, 45911402, 45911403) for **INDOXACARB**. The study is classified as **Acceptable/Guideline.**

CITATION:

1. Fasano, W.J. (2002) DPX-MP062 30WG (300g indoxacarb/kg): *In vivo* dermal absorption in the rat. E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE. Laboratory Project Id: DuPont-11303, December 4, 2002. MRID 45911402. Unpublished

2. Fasana, W.J. (2002) DPX-MP062 30WG (300g indoxacarb/kg): *In*

vivo dermal absorption in the rat (supplement). E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE. Laboratory Project Id: DuPont-11303, December 18, 2002. MRID 45911403. Unpublished

3. Fasano, W.J. (2002) DPX-MP062 30WG (300g indoxacarb/kg): *In vitro* dermal kinetics in the rat. E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE. Laboratory Project Id: DuPont-11302, December 4, 2002. MRID 45911401. Unpublished

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 45911402), [1-^{14}C-indanone] DPX-MP062 (99.2% radiochemical purity, lot/batch #3381277) was administered to the shaved intact skin (10.5 cm^2) of 4 male Crl:CD®(SD)IGS BR rats/time point/dose at dose levels of 13.3 $\mu g/cm^2$ (aqueous dilution) or 2000 $\mu g/cm^2$ (commercial formulation) for a 6-hour exposure period. After 6 hours, the skin of each rat was washed, and 4 rats/dose were sacrificed (0 hours post-exposure) for examination of dermal absorption. The remaining 4 rats/dose were sacrificed at 162 hours post-exposure to determine further post-exposure absorption. The maximum potential absorption at 14-days post-dose was predicted using an exponential saturation modeling approach of non-linear curve fitting (MRID 45911403) with the cumulative excretion data from the rats sacrificed 162 hours post-exposure. Additionally, an *in vitro* study was conducted comparing dermal absorption during a 6-hour exposure in rat and human skin, utilizing the same dosing regimen as in the *in vivo* study, except that skin samples were examined 12 hours (instead of 162 hours) post-exposure (MRID 45911401).

For the *in vivo* study in the rat, total recovery of the applied dose ranged from 96.9-98.8%. During the 6-hour exposure period, absorption was minimal, with 0.08% of the low dose and 0.19% of the high dose being absorbed. At the end of the 6-hour exposure, skin washing removed 75.5-83.2% of the low dose and 82.2-85.1% of the high dose. Including radioactivity remaining in tape-stripped skin, the total absorbable dose was 0.94% at the low dose and 0.41% at the high dose after a 6-hour exposure. At the end of the 162-hour post-exposure period (168 hour post-dose), there were increases in the absorbed dose for both the low dose (4.76%) and high dose (0.87% dose), but the total absorbable dose remained low at 4.91% of the low dose and 0.88% of the high dose.

Using excretion data from the *in vivo* study, the model-predicted maximum absorption at 14 days post-dose was 6.67% for the low dose and 1.06% for the high dose. These dermal absorption estimates for rats are considered conservative because (i) the model-predicted absorption values included test substance remaining in the carcass at 168 hours post dose that would likely have been excreted by 14 days, and (ii) the collection interval of 7 days likely does not include loss of test substance from the application site due to desquamation.

The *in vitro* study demonstrated that absorption was minimal and higher for rat skin than human skin

at both doses. Total recovery of the applied dose ranged from 90.3-105.5%. At the low dose during the 6-hour exposure period, the rate of dermal penetration of the test substance was 10-fold faster in rat skin compared to human skin, resulting in a total absorption in rat skin that was 7.7-fold higher than human skin. The high dose penetrated rat skin only. At the end of the 6-hour exposure, skin washing removed more than twice the amount of the applied dose from human skin than from rat skin at the low dose and removed the majority (96.1-101.2%) of the dose, irrespective of the species, at the high dose. In contrast, tape-stripping after the 6-hour exposure removed twice the amount of applied dose in rat skin than in human skin at both doses, and the remaining tape-stripped skin contained levels in the rat skin that were 50-fold higher at the low dose and 5-fold higher at the high dose, compared to human skin. Thus, the total absorbable dose was higher in rat skin than in human skin at the end of the 6-hour exposure. During the 12-hour post exposure period, there was an increase in absorption from rat skin, concomitant with decreased radioactivity in skin, indicating that radioactivity in the rat skin remained available for continued absorption. Continued absorption from the washed human skin was not evident.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

Note: Copy of the DER is attached.

DATA EVALUATION RECORD

INDOXACARB

Study Type: §85-2a; Dermal Penetration Study in Rats

Work Assignment No. 1-01-28 (MRIDs 45911402, 45911403, and 45911401).

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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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Health Effects Division (7509C) **Date** 9/13/04
EPA Work Assignment Manager: P.V. Shah, Ph.D. **Signature:** P.V. Shah
Registration Action Branch 1, Health Effects Division (7509C) **Date** 1/24/05

DATA EVALUATION RECORD

STUDY TYPE: Rodent *In Vivo* Dermal Penetration Study - Rat; OPPTS 870.7600 [§85-2]; OECD none.

PC CODE: 067710 **DP BARCODE:** 300062
TXR#: 0052429 **SUBMISSION NO.:** Not provided

TEST MATERIAL (RADIOCHEMICAL PURITY): Indoxacarb technical (>99%)

SYNONYMS: methyl (*S*)-N-[7-chloro-2,3,4a,5-tetrahydro-4a(methoxycarbonyl)indeno [1,2-*e*][1,3,4]oxadiazin-2-ylcarbonyl]-4'-(trifluoromethoxy)carbanilate

CITATION: Fasano, W.J. (2002) DPX-MP062 30WG (300g indoxacarb/kg): *In vivo* dermal absorption in the rat. E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE. Laboratory Project Id: DuPont-11303, December 4, 2002. MRID 45911402. Unpublished

Fasana, W.J. (2002) DPX-MP062 30WG (300g indoxacarb/kg): *In vivo* dermal absorption in the rat (supplement). E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE. Laboratory Project Id: DuPont-11303, December 18, 2002. MRID 45911403. Unpublished

Fasano, W.J. (2002) DPX-MP062 30WG (300g indoxacarb/kg): *In vitro* dermal kinetics in the rat. E.I. du Pont de Nemours and Company, Haskell Laboratory for Health and Environmental Sciences, Newark, DE. Laboratory Project Id: DuPont-11302, December 4, 2002. MRID 45911401. Unpublished

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, DE

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 45911402), [1-^{14}C-indanone] DPX-MP062 (99.2% radiochemical purity, lot/batch #3381277) was administered to the shaved intact skin (10.5 cm^2) of 4 male Crl:CD®(SD)IGS BR rats/time point/dose at dose levels of 13.3 µg/cm^2 (aqueous dilution) or 2000 µg/cm^2 (commercial formulation) for a 6-hour exposure period. After 6 hours, the skin of each rat was washed, and 4 rats/dose were sacrificed (0 hours post-exposure) for examination of dermal absorption. The remaining 4 rats/dose were sacrificed at 162 hours post-exposure to determine further post-exposure absorption. The maximum potential absorption at 14-days post-dose was predicted using an exponential

saturation modeling approach of non-linear curve fitting (MRID 45911403) with the cumulative excretion data from the rats sacrificed 162 hours post-exposure. Additionally, an *in vitro* study was conducted comparing dermal absorption during a 6-hour exposure in rat and human skin, utilizing the same dosing regimen as in the *in vivo* study, except that skin samples were examined 12 hours (instead of 162 hours) post-exposure (MRID 45911401).

For the *in vivo* study in the rat, total recovery of the applied dose ranged from 96.9-98.8%. During the 6-hour exposure period, absorption was minimal, with 0.08% of the low dose and 0.19% of the high dose being absorbed. At the end of the 6-hour exposure, skin washing removed 75.5-83.2% of the low dose and 82.2-85.1% of the high dose. Including radioactivity remaining in tape-stripped skin, the total absorbable dose was 0.94% at the low dose and 0.41% at the high dose after a 6-hour exposure. At the end of the 162-hour post-exposure period (168 hour post-dose), there were increases in the absorbed dose for both the low dose (4.76%) and high dose (0.87% dose), but the total absorbable dose remained low at 4.91% of the low dose and 0.88% of the high dose.

Using excretion data from the *in vivo* study, the model-predicted maximum absorption at 14 days post-dose was 6.67% for the low dose and 1.06% for the high dose. These dermal absorption estimates for rats are considered conservative because (i) the model-predicted absorption values included test substance remaining in the carcass at 168 hours post dose that would likely have been excreted by 14 days, and (ii) the collection interval of 7 days likely does not include loss of test substance from the application site due to desquamation.

The *in vitro* study demonstrated that absorption was minimal and higher for rat skin than human skin at both doses. Total recovery of the applied dose ranged from 90.3-105.5%. At the low dose during the 6-hour exposure period, the rate of dermal penetration of the test substance was 10-fold faster in rat skin compared to human skin, resulting in a total absorption in rat skin that was 7.7-fold higher than human skin. The high dose penetrated rat skin only. At the end of the 6-hour exposure, skin washing removed more than twice the amount of the applied dose from human skin than from rat skin at the low dose and removed the majority (96.1-101.2%) of the dose, irrespective of the species, at the high dose. In contrast, tape-stripping after the 6-hour exposure removed twice the amount of applied dose in rat skin than in human skin at both doses, and the remaining tape-stripped skin contained levels in the rat skin that were 50-fold higher at the low dose and 5-fold higher at the high dose, compared to human skin. Thus, the total absorbable dose was higher in rat skin than in human skin at the end of the 6-hour exposure. During the 12-hour post exposure period, there was an increase in absorption from rat skin, concomitant with decreased radioactivity in skin, indicating that radioactivity in the rat skin remained available for continued absorption. Continued absorption from the washed human skin was not evident.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.7600; OECD none) for a dermal penetration study in rats.

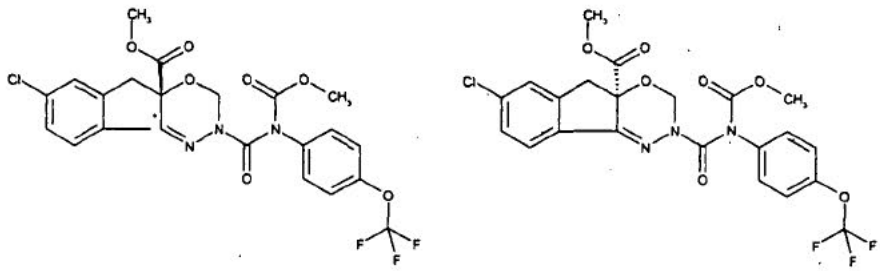
COMPLIANCE: Signed and dated Data Confidentiality, GLP, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: [indanone-1-^{14}C] DPX-MP062

Description:	Formulated End use product; water dispersible granules (WDG)
Lot/Batch #:	3381277
Chemical Purity:	39.2% a.i. (30.4% DP-KN128, active isomer)
Compound stability:	Not reported
CAS # for TGAI:	144171-61-9 for DPX-MP062 173584-44-6 for the active isomer (DPX-KN128) 185608-75-7 for the inactive isomer (IN-KN127)
Structure:	S-(+) enantiomer R-(-) enantiomer



* indicates position of ^{14}C-label within molecule

Vehicle/solvent used:	Water was the vehicle for the aqueous dilution (low dose), and physiological saline was used as the vehicle for the granular concentrate (high dose).
Specific activity:	51.64 µCi/mg (reported); 58.2 µCi/mg (verified)
Radiochemical purity:	99.2% (radioactivity was incorporated in the active S-isomer)
Source:	Perkin Elmer

2. Relevance of test material to proposed formulation(s): The test substance (DPX-MP062) is the commercially formulated end-use product, containing nominal concentrations of 30% S-(+) enantiomer (DPX-KN128), 10% R-(-) enantiomer (IN-KN127), and 60% inert ingredients, including [redacted]

3. Test animals

Species:	Rats, male	
Strain:	Crl:CD®(SD)IGS BR	
Approximate age/weight at study initiation:	Approximately 6-8 weeks; 190.1-216.3 g	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	Individually, in all-glass metabolism cages	
Diet:	Certified Rodent LabDiet® #5002 (PMI Nutrition International, Inc.), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	23 ± 1°C
	Humidity:	40-60%
	Air changes:	Not reported
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	At least 6 days	

Inert ingredient information may be entitled to confidential treatment

B. STUDY DESIGN

1. Dose

Rationale: It was stated that the concentrations and application rates were designed to mimic potential field-use exposures. The high dose was selected to represent exposure of mixers and loaders to an undiluted commercial WDG formulation, and the low dose was selected to represent exposure of applicators to the water-diluted formulation used for field application.

Nominal doses: 2000 and 13.3 $\mu g/cm^2$

Actual doses: Low dose, 11 $\mu g/cm^2$; high dose, 1838-1857 $\mu g/cm^2$

Dose volume: 10 $\mu L/cm^2$

Duration of exposures (time from dose to skin wash): 6 hours

Termination periods (time from dose to sacrifice): In the *in vivo* study in the rat (MRID 45911402), 4 rats/dose were sacrificed at the end of the 6-hour exposure period, and the remaining 4 rats/dose were sacrificed 168 hours post-dose (162 hours post-exposure).

In the *in vitro* study using rat and human skin (MRID 45911401), 4 skin samples/species/dose were collected and processed immediately following the 6-hour exposure (0-hour post exposure) and at 18 hours post-exposure.

Number of animals/group: 4 rats or skin samples (rat or human)/time point/dose

2. Animal/tissue preparation: For the *in vivo* study in the rat (MRID 45911402), animals were anesthetized 24 hours before dosing and the back and shoulders of each rat was shaved and washed with 2% Ivory® soap solution in water. A porous Expandover® bandage was wrapped around the shaved area to prevent contamination, and the rats were fitted with cervical collars. On the day of dosing, animals were again anesthetized, and the protective gauze wrap was removed. One or more O-rings (stacked upon one another) were glued to the shaved area on the back of the rat, provided an exposure area of approximately 10.5 cm^2.

For the *in vitro* study (MRID 45911401) using isolated skin samples, rats were sacrificed by carbon dioxide asphyxiation, and the fur was shaved from the dorsal area of each animal. Skin from the shaved area was excised, held briefly on wet ice, and frozen at approximately -20°C until processed. Samples of human skin were obtained from the International Institute for the Advancement of Medicine and were stored frozen at approximately -20°C until further processing. Frozen samples were thawed at room temperature, cut to a thickness of 450 μM, and stored at 0-10°C until use. Using an *in vitro* diffusion cells assembly (Figure 1 in Appendix of this DER), the skin membrane was mounted onto the top of the receptor chamber with the epidermal surface facing up, and the donor chamber was placed over the skin section and clamped into place. The integrity of each membrane was assessed by measurement of electrical

resistance prior to application of the test substance, and only skin samples with a resistance of ≥6kΩ (rat) or ≥17kΩ (human) were used.

3. Dose preparation, administration, and quantification

Preparation: The source of radioactivity in the formulated doses was from [1-^{14}C-indanone] DPX-MP062. Both formulated samples were stored at ≤-10°C until use.

The neat formulation was prepared by first blending radiolabeled and non-radiolabeled DPX-MP062 together with [redacted] followed by the addition of a small volume of acetone. The sample, or blend base, was mixed thoroughly and the acetone evaporated before proceeding. Once the acetone had evaporated, [redacted] were added, the sample mixed to a homogeneous consistency, and then air-milled at approximately 60 psi using a Fluid Energy Jet-Mill (Fluid Energy Aljet, Telford, PA). The milled sample was collected and deionized water added on a dry-basis at 43%, mixed, and the water evaporated at 70°C until a consistent weight was achieved in the final product.

The aqueous dilution was prepared by first blending radiolabeled DPX-MP062 with [redacted] and acetone. The sample was mixed and the acetone evaporated at room temperature (blend base). To this sample, a solution containing [redacted] was added, followed by the addition of grinding media (i.e., 0.8-1.0 mm diameter glass beads). A mixing impeller was inserted into the sample, and the sample milled at approximately 4000 rpm for 154 minutes. The milled sample, including the glass beads, was quantitatively transferred, with successive deionized water rinses, from the milling vial into a large glass vial.

Table 1. Dosing for in vivo rat study [a]

Nominal Dose (µg/cm²)	Amount of Indoxacarb in dosing solution (mg/animal)		Specific Activity (µCi/mg)	Actual Dose (µg/cm²)
	Radio-labeled	Non-labeled		
2000	0.33	19.67	0.97	1838-1857
13.3	0.116	0	58.2	11.0-11.7

a Data were obtained from: pages 17, 29, 30, and 32 of MRID 45911402; pages 32 and 37 of MRID 45911401.

Application: For the *in vivo* study in the rat (MRID 45911402), the dose formulations were applied to the skin surface as a single application distributed evenly over the exposure site inside the O-ring(s). The formulated WDG (40% a.i.) was applied at a rate of 5 mg/cm², following the addition of physiologic saline (0.9%) applied to the skin surface at a rate of 10 µL/cm². The aqueous dilution was applied at a rate of 10 µL/cm². Following dose administration, the application skin site was protected with a non-occlusive rigid mesh covering glued to the top of the O-ring spacers, and the Expandover® bandage was replaced for the 6-hour exposure.

For the *in vitro* study (MRID 45911401), the exposure area (0.64 cm²) was dosed via the donor chamber in a manner identical to the *in vivo* study.

Quantification: The actual dose of neat WDG concentrate administered to the skin was measured by weight. The actual dose of aqueous dilution administered to the skin was measured by radioassay of replicate mock doses and calculating a mean.

The homogeneity and amount of radiolabeled DPX-MP062 (μCi/g) in each dose formulation was determined by triplicate analyses via liquid scintillation counting (LSC). The concentrations of DPX-KN128 and IN-KN127 in each dose formulation were determined by triplicate analyses via HPLC. The radiochemical stability of [1-^{14}C]DPX-MP062 was determined in neat and diluted formulations using fraction collection followed by LSC.

4. **Skin wash (pre-sacrifice):** For the *in vivo* study in the rat (MRID 45911402), at 6 hours post-dose, the gauze wrap and protective cover were removed and retained for analysis. Using natural sponges, the application site of each rat was washed with 2% Ivory® soap solution, rinsed with water, and dried. The skin wash and sponges were collected for analysis.

For the *in vitro* study (MRID 45911401), the skin samples were washed at 6 hours post-dose with 2% Ivory® soap solution and rinsed with water. The donor chamber remained clamped in place during the skin wash.

5. **Sample collection:** For the *in vivo* study in the rat (MRID 45911402), urine and feces were collected during the 6-hour exposure period and for the following intervals in rats not sacrificed at the end of the exposure period: 6-12, 12-24, 24-48, 48-72, 72-96, 120-144, and 144-168 hours post-dose. At 6 hours post-dose (0 hours post-exposure), 4 rats/dose were sacrificed by carbon dioxide inhalation and exsanguination via cardiac puncture. The remaining 4 rats/dose were sacrificed at 168 hours (162 hours post-exposure). Whole blood was retained on wet ice or refrigerated until centrifugation to separate plasma from blood cells. The application site was excised and tape-stripped using Leukotape® P (Beiersdorf, Hamburg, Germany). Each tape strip, the remaining skin piece, and an area of non-dosed skin were collected separately. Following sacrifice, each metabolism cage was washed (using a dilute soap solution and acetone rinse) and the cage wash collected.

In the *in vitro* study (MRID 45911401), duplicate 50 μL samples of receptor fluid were taken from the receptor chambers during the exposure period at 0.5, 1, 2, 4, and 6 hours post-dose and placed directly into scintillation vials. Fresh receptor fluid (equivalent to the sample volume) was added to the chamber at sampling to maintain a constant volume. At termination, the donor chamber was removed and rinsed with methanol directly into a scintillation vial. The skin was removed from the chamber, tape-stripped, and retained for analyses in a manner identical to the *in vivo* study.

6. **Sample preparation and analysis:** Details of sample processing and analyses are included in Table 2.

Table 2. Sample preparation and analyses [a]

Sample Media	Preparation Details
Whole blood	A portion was centrifuged to produce plasma and red blood cells. Aliquots were combusted
Plasma	Aliquots were added directly to a liquid scintillation fluid
Red blood cells	Aliquots were combusted
Feces	Homogenized in water. Aliquots were combusted
Residual food	
Carcass	
Urine	Aliquots were added directly to liquid scintillation fluid without further processing.
Cage wash	
Skin at application site [b]	Digested in heated Soluene®-350 and added directly to liquid scintillation fluid
Non-dosed skin	
Sponge pieces	
Protective mesh cover	Extracted with methanol. Aliquots were added directly to liquid scintillation fluid
Gauze wrap	
O-ring spacers	
Tape strips [b]	

a Obtained from page 21 in MRID 45911402, page 23 in MRID 45911401.
b Applies to samples from the *in vivo* study in rats (MRID 45911402) and the *in vitro* study with rat and human skin (MRID 45911401).

Liquid scintillation samples were counted for 10 minutes or until 160,000 disintegrations were accumulated, whichever came first. For each sample, the limit of detection was taken as twice the background disintegration rate, and the limit of quantitation was taken as three times the background disintegration rate.

The following definitions were provided for the *in vivo* study in the rat (MRID 45911402):

The absorbed dose was defined as the sum of the applied dose detected in urine, feces, cage wash, residual food, non-dosed skin, whole blood, red blood cells, and plasma.

The total absorbable dose was defined as the sum of the absorbed dose plus the radioactivity in the tape-stripped skin, which is potentially available for absorption.

The unabsorbed dose was defined as the sum of the applied dose detected in the body wrap, protective cover, skin wash, site enclosure, and tape strips.

The following definitions were provided for the *in vitro* study (MRID 45911401):

The absorbed dose was defined as the percent of the applied dose detected in the receptor fluid.

The absorbable dose was defined as the sum of the absorbed dose plus the tape-stripped skin.

The unabsorbed dose was defined as the sum of the applied dose detected in the skin wash, tape strips, and donor chamber rinse.

7. Model-predicted excretion at 14 days post-dose: The actual cumulative excretion data from the 168 hour post-dose group in the *in vivo* study in the rat (MRID 45911402) were used to predict the maximum excretion at 14 days post-dose employing an exponential saturation modeling approach (MRID 45911403) using Microcal™ Origin™, v. 7.0 (OriginLab Corporation, Northampton, MA). Non-linear curve fitting involved iteration using the least squares method to best-fit the excretion data to the following equation:

$Y = A[1-e^{-B(X-C)}]$, where:

Y = amount recovered in excreta at the post-dose time X.
A = maximum dose recovered in excreta at asymptote beyond the range of the actual data.
B = first-order elimination rate constant.
C = lag time from dosing to initial excretion.

II. RESULTS

A. SIGNS AND SYMPTOMS OF TOXICITY: No mortalities or clinical signs of toxicity were observed in the *in vivo* study in the rat.

B. DERMAL ABSORPTION: For the *in vivo* study in the rat, total recovery of the applied dose ranged from 96.9-98.8% (Table 3). During the 6-hour exposure period, absorption was minimal, with 0.08% of the low dose and 0.19% of the high dose being absorbed. At the end of the 6-hour exposure, skin washing of all animals removed 75.5-83.2% of the low dose and 82.2-85.1% of the high dose. Tape stripping of treated skin from animals terminated at 0 hours post-exposure removed another 13.98% and 6.29% of the low and high doses, respectively. Total unabsorbed dose (including tape strips) following the 6-hour exposure accounted for 96.8-97.9% of the applied dose. Including radioactivity remaining in the tape-stripped skin and available for potential absorption, the total absorbable dose immediately following exposure accounted for 0.94% and 0.41% for the low and high doses, respectively. Continued absorption of dosed radioactivity following skin washing was evident, with 4.76% and 0.87% of the dose being absorbed by the low and high dose rats, respectively, by 162 hours post exposure. Concomitant with the increase in absorption, there was a decline in radioactivity (0.7% low dose; 0.21% high dose) associated with the tape-stripped skin. Although the declines in radioactivity in the tape-stripped skin do not account for the larger increases in absorption, tape stripping of the treated skin at 162 hours post-exposure indicates that substantial amounts of radioactivity (low dose, 15.8%; high dose, 2.14%) remained on the surface of the skin following washing. Although the study authors characterized the radioactivity associated with the tape strips as "unabsorbed", apparently a portion of the radioactivity on the skin surface is available for further absorption.

Table 3. Summary of percent applied dose following a 6-hour exposure to a single dermal dose of [1-^{14}C-indanone] DPX-MP062 *in vivo* in the rat [a]

Sample	Dose (μg/cm^2)			
	13.3		2000	
Hours post-dose	0	162	0	162
Urine	0.02 ± 0.01	1.80 ± 0.62	<0.01	0.23 ± 0.10
Feces	ND	2.01 ± 1.08	ND	0.26 ± 0.30
Cage wash	ND	0.51 ± 0.25	0.04 ± 0.01	0.19 ± 0.21
Residual food	ND	0.12 ± 0.01	ND	0.04
Non-dosed skin	ND	ND	0.05	0.01 ± 0.01
Carcass	0.26	0.35 ± 0.06	0.21 ± 0.06	0.18 ± 0.12
Whole blood	<0.01 ± <0.01	0.01 ± 0.01	ND	<0.01 ± <0.01
RBC (terminal)	ND	<0.01 ± <0.01	ND	ND
Plasma (terminal)	ND	<0.01 ± <0.01	ND	<0.01 ± <0.01
Total dose absorbed	**0.08 ± 0.14**	**4.76 ± 1.35**	**0.19 ± 0.11**	**0.87 ± 0.75**
Tape-stripped skin	0.86 ± 0.51	0.16 ± 0.03	0.23 ± 0.27	0.02 ± 0.01
Total dose absorbable	**0.94 ± 0.62**	**4.91 ± 1.33**	**0.41 ± 0.38**	**0.88 ± 0.76**
Body wrap	ND	0.15 ± 0.21	4.66 ± 7.41	2.70 ± 0.31
Mesh cover	0.31	0.63 ± 0.77	0.57 ± 0.30	0.58 ± 0.11
Skin wash - sponges	83.15 ± 7.05	75.53 ± 5.79	82.16 ± 10.22	85.11 ± 4.85
O-ring	0.68 ± 0.55	1.64 ± 1.03	3.14 ± 1.12	5.50 ± 2.40
Tape strips	13.98 ± 3.90	15.77 ± 7.98	6.29 ± 3.35	2.14 ± 1.35
Total dose unabsorbed	**97.88 ± 3.64**	**93.68 ± 4.98**	**96.83 ± 3.00**	**96.02 ± 2.43**
Total dose recovered	**98.82 ± 4.19**	**98.59 ± 4.06**	**97.24 ± 2.80**	**96.90 ± 1.80**

a Data were obtained from Tables 3 and 5 on pages 31 and 33 of MRID 45911402.
ND Not detected.

Based on the actual amount of radioactivity recovered in excreta of rats from 0-168 hours post dose from the *in vivo* rat study, an exponential saturation model was used to predict maximum absorption after 14 days. The following parameters were selected to model excretion from the low dose group (A=7.11%, B= 0.0049%/h, and C=2.42h) and high dose group (A=0.80%, B=0.0053%/h, and C=-15.3h). Graphs depicting the fit of the modeled data to the actual excretion data are presented in Figure 2 of the Appendix to this DER.

Using the following equation, $Y = A[1\text{-}e^{-B(X-C)}]$, the model-predicted excretion of radioactivity was calculated to be 5.71% and 0.68% dose for the low and high dose groups, respectively, at 14 days post dose (Table 4). Combining the modeled excreta data with the radioactivity found in cage wash, carcass, skin (non-treated), residual food, and blood at 168 hours post-dose, the maximum total absorption predicted for low and high dose rats is 6.67% and 1.06% dose, respectively, at 14 days post dose.

Table 4. Model-predicted maximum absorbable dose (% applied dose) at 14 days, following a 6-hour exposure to a single dermal dose of [1-^{14}C-indanone] DPX-MP062 *in vivo* in the rat [a]

Sample	Dose (μg/cm^2)	
	13.3	2000
Excreta [b]	5.71	0.68
Cage wash [c]	0.50 ± 0.25	0.19 ± 0.21
Residual food [c]	0.12 ± 0.01	0.04
Non-dosed skin [c]	ND	0.01 ± 0.01
Carcass [c]	0.35 ± 0.06	0.18 ± 0.12
Whole blood [c]	0.01 ± 0.01	<0.01 ± <0.01
Total predicted dose absorbed	**6.67 ± 0.25**	**1.06 ± 0.36**

a Data were obtained from Tables 2 and 4 on pages 18 and 20 of MRID 45911403.
b Model predicted value for excreta at 14 days.
c Data on radioactivity in each fraction at 7 days post-dose.
ND Not detected

For the *in vitro* study with rat and human skin, total recovery of the applied dose ranged from 90.3-105.5% (Table 5). Periodic sampling of the receptor fluid during the 6-hour *in vitro* exposure period, indicated that the rate of dermal penetration of the test substance at the **low dose** was 10-fold faster in rat skin (0.06 μg equiv/cm^2/hour) compared to human skin (0.006 μg equiv/cm^2/hour). Thus, the total absorption for rat skin (2.92% dose) was 7.7-fold higher than human skin (0.38% dose). At the end of the 6-hour exposure, washing of all samples removed more approximately twice the amount of the applied dose from human skin (61.0-62.7%) than from rat skin (25.5-35.9%). Subsequent tape-stripping of skin sampled at 0-hour post-exposure removed an additional 52.4% dose from rat skin and 26.2% dose from human skin. Radioactivity remaining in the tape-stripped skin was potentially available for absorption and was 50 fold higher in the rat skin (12.9% dose) than in human skin (0.27%). Thus, the total absorbable dose was higher in rat skin (15.8%) than in human skin (0.36%) at the end of the 6-hour exposure. Following the 12-hour post exposure period (18 hours post-dose), there was an increase in absorption from rat skin of 5.2% dose with a concomitant decrease of 5.8% dose in the tape-stripped skin, indicating that radioactivity in the rat skin remained available for continued absorption. Continued absorption from the washed human skin was not evident, although the low levels and variability of radioactivity remaining in human skin precluded detecting any meaningful movement of radioactivity.

During the 6-hour *in vitro* exposure period, the **high dose** penetrated rat skin at a rate of 0.34 µg equiv/cm^2/hour, with a total absorption of 0.09%. Any absorption in human skin was below the limit of detection. At the end of the 6-hour exposure period, skin washing removed the majority of the dose in rat (101.2-103.2%) and human (96.1-98.9%) skin. Tape-stripping immediately after after the 6-hour exposure removed an additional 1.32% dose from rat skin and 0.66% dose from human skin. Radioactivity remaining in tape-stripped skin was 5 fold higher in the rat skin (0.30% dose) compared to human skin (0.06%). Thus, the total absorbable dose was higher in rat skin (0.32%) than in human skin (0.06%) at the end of the 6-hour exposure. As in the low dose group, continued absorption of radioactivity from washed rat skin was evident in the high dose group. Although small, there was an increase in absorption of 0.21% dose, along with a quantitative decrease of 0.22% dose in the tape-stripped skin. Absorption of radioactivity from washed human skin was not evident.

Table 5. Summary of percent applied dose following a 6-hour *in vitro* exposure of [1-^{14}C-indanone] DPX-MP062 in rat and human skin [a]

Sample	Dose (µg/cm^2)			
	13.3		2000	
Hours post-dose	0	18	0	18
Rat skin				
Total dose absorbed (receptor fluid)	**2.92 ± 2.51**	**8.11 ± 2.41**	**0.09**	**0.30 ± 0.12**
Tape-stripped skin	12.9 ± 4.71	7.07 ± 10.1	0.30 ± 0.21	0.08 ± 0.05
Total dose absorbable	**15.8 ± 5.29**	**15.2 ± 8.62**	**0.32 ± 0.19**	**0.38 ± 0.15**
Skin wash	25.5 ± 8.21	35.9 ± 10.4	101.2 ± 7.57	103.2 ± 3.11
Donor chamber	0.55 ± 0.57	2.28 ± 4.22	0.07 ± 0.03	0.08 ± 0.05
Tape strips	52.4 ± 3.30	41.0 ± 8.15	1.32 ± 0.95	1.78 ± 0.88
Total dose unabsorbed	**78.5 ± 6.32**	**79.2 ± 11.0**	**102.6 ± 8.19**	**105.1 ± 3.65**
Total dose recovered	**94.3 ± 3.01**	**94.3 ± 2.73**	**102.9 ± 8.01**	**105.5 ± 3.71**
Human skin				
Total dose absorbed (receptor fluid)	**0.38**	**0.45 ± 0.15**	**ND**	**ND**
Tape-stripped skin	0.27 ± 0.13	0.42 ± 0.29	0.06 ± 0.03	0.08 ± 0.07
Total dose absorbable	**0.36 ± 0.22**	**0.87 ± 0.40**	**0.06 ± 0.03**	**0.08 ± 0.07**
Skin wash	61.0 ± 15.3	62.7 ± 8.46	96.1 ± 9.37	98.9 ± 2.47
Donor chamber	2.73 ± 5.07	0.20 ± 0.10	0.05 ± 0.05	0.11 ± 0.16
Tape strips	26.2 ± 8.82	27.3 ± 6.49	0.66 ± 0.11	0.99 ± 0.56
Total dose unabsorbed	**89.9 ± 6.38**	**90.2 ± 2.01**	**96.8 ± 9.38**	**100.0 ± 2.66**
Total dose recovered	**90.3 ± 6.19**	**91.1 ± 1.72**	**96.8 ± 9.35**	**100.0 ± 2.66**

a Data were obtained from Tables 3, 5, 9, and 11 on pages 34, 36, 40, and 42 of MRID 45911401.
ND Not detected

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: In the *in vivo* study in the rat, total absorption was low following the 6-hour exposure duration, with higher maximum absorption for the aqueous dilution (4.91%) than for the neat formulation (0.88%). The model predicted total absorption 14 days post-exposure was estimated to be 6.67% of the applied dose for the aqueous dilution and 1.06% dose for the undiluted concentrate. The *in vitro* studies demonstrated that the absorption of either dose formulation would be minimal and that absorption was greater in rat skin than in human skin.

B. REVIEWER COMMENTS: For the *in vivo* study in the rat, total recovery of the applied dose ranged from 96.9-98.8%. During the 6-hour exposure period, absorption was minimal, with 0.08% of the low dose and 0.19% of the high dose being absorbed. At the end of the 6-hour exposure, skin washing removed 75.5-83.2% of the low dose and 82.2-85.1% of the high dose. Including radioactivity remaining in tape-stripped skin, the total absorbable dose was 0.94% at the low dose and 0.41% at the high dose after a 6-hour exposure. At the end of the 162-hour post-exposure period (168 hour post-dose), there were increases in the absorbed dose for both the low dose (4.76%) and high dose (0.87%), but the total absorbable dose remained low at 4.91% of the low dose and 0.88% of the high dose.

The model-predicted absorption at 14 days post-dose, based on data collected from rats for 168 hour post-dose, was 6.67% at the low dose and 1.06% at the high dose. These dermal absorption estimates for rats are considered conservative because (i) the model-predicted absorption values included test substance remaining in the carcass at 168 hours post dose that would likely be excreted, and (ii) the collection interval of 7 days likely does not include loss of test substance from the application site due to desquamation.

The *in vitro* study demonstrated that absorption was minimal and that absorption was higher in rat skin compared to human skin at both doses. Total recovery of the applied dose ranged from 90.3-105.5%. At the low dose during the 6-hour exposure period, the rate of dermal penetration of the test substance was 10-fold faster in rat skin compared to human skin, resulting in a total absorption in rat skin that was 7.7-fold higher than human skin. The high dose penetrated rat skin only. At the end of the 6-hour exposure, skin washing removed more than twice the amount of the applied dose from human skin than from rat skin at the low dose and removed the majority (96.1-101.2%) of the dose, irrespective of the species, at the high dose. In contrast, tape-stripping after the 6-hour exposure removed twice the amount of applied dose in rat skin than in human skin at both doses, and the remaining tape-stripped skin contained levels in the rat skin that were 50 fold higher at the low dose or 5 fold higher at the high dose, compared to human skin. Thus, the total absorbable dose was higher in rat skin than in human skin at the end of the 6-hour exposure. In the 12-hour post exposure period (18 hours post-dose), the percent of the applied dose absorbed did not appreciably change in rat or human skin.

C. STUDY DEFICIENCIES: The following study deficiencies were noted in this dermal penetration study:

- It was stated that the concentration, homogeneity, and stability of the test substance in the dosing preparations were verified analytically; however, these data were not provided.

- Only two dose levels were used (0.013 and 2 mg/cm^2), instead of the minimum three dose levels required by the guidelines. In addition, although the high dose was designed to mimic worker exposure to the undiluted end-use product, the high dose exceeded the maximum dose (1 mg/cm^2) typically considered practical by the Agency.

- The effect of dose concentration on penetration of the test substance could not be determined as the two dose levels used different vehicles for dosing (dilute aqueous suspension vs. an undiluted commercial end use product).

- Only a single exposure interval (6 hours) was used in the study, and it did not reflect a typical daily worker exposure of 8-10 hours. In addition, the use of only two post-exposure sampling intervals (0-hour and 162-hour) provided limited data.

However, despite these deficiencies, the general purpose of this study was fulfilled, as the data demonstrated that dermal absorption of indoxacarb was limited (<7% dose) following a 6-hour exposure to either the diluted field spray or the concentrated end-use product.

APPENDIX

Figure 1. Schematic of the static diffusion cell apparatus for *in vitro* exposure of skin

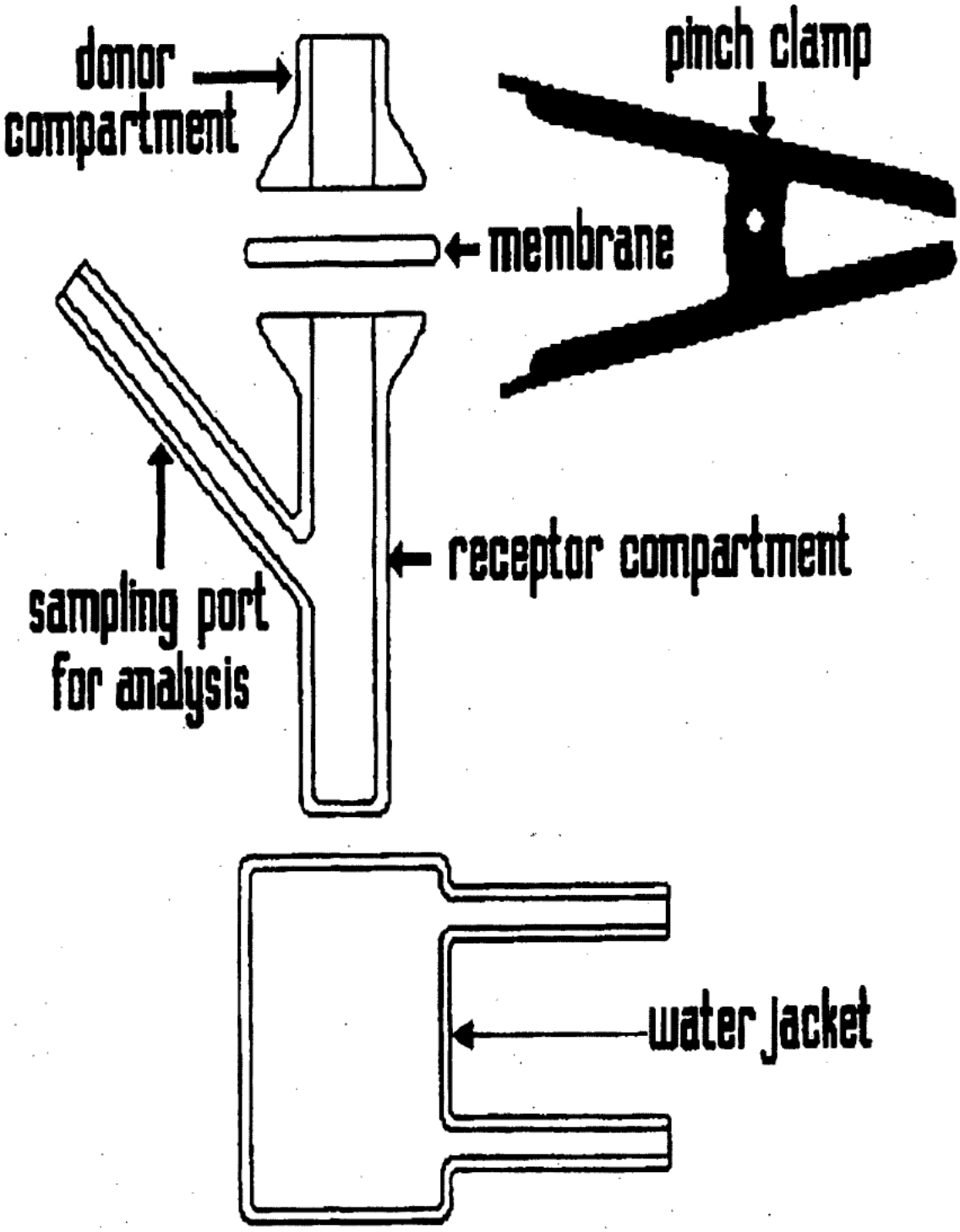


Fig 2. Exponential saturation model fit of excretion data from rats in the 162 hour post-exposure group to predict maximum absorption